SUMMARY OF SAFETY AND PROBABLE BENEFIT

I. GENERAL INFORMATION

Device Generic Name:	Intravascular Intracranial Stent Intracranial Dilatation Catheter
Device Trade Name:	NEUROLINK® System, including: NEUROLINK® Stent & Delivery Catheter NEUROLINK® Balloon Dilatation Catheter
Applicant's Name and Address:	Guidant Corporation 3200 Lakeside Drive Santa Clara, CA 95052

Humanitarian Device Exemption (HDE) Number: H010004

Date of Humanitarian Use Device Designation: September 5, 2001

Date of Panel Recommendation: Not applicable. See Section XII.

Date of Good Manufacturing Practices (GMP) Inspection:

Santa Clara, CA:	April 26, 2001
Temecula, CA:	May 23, 2001

Date of notice of Approval to the Applicant: August 9, 2002

II. INDICATIONS FOR USE

The NEUROLINK® System is indicated for the treatment of patients with recurrent intracranial stroke attributable to atherosclerotic disease refractory to medical therapy in intracranial vessels ranging from 2.5 to 4.5 mm in diameter with $\geq$ 50% stenosis and that are accessible to the stent system.

III. CONTRAINDICATIONS

NEUROLINK® Stent & Delivery Catheter and NEUROLINK® Balloon Dilatation Catheter are contraindicated for use in:

- Lesions that are highly calcified or otherwise could prevent access or appropriate expansion of the Stent.
- Patients in whom anticoagulant and/or antiplatelet therapy is contraindicated.

IV. WARNINGS AND PRECAUTIONS

See *Warnings and Precautions* in the final labeling (Instructions for Use) for the NEUROLINK® Stent & Delivery Catheter and NEUROLINK® Balloon Dilatation Catheter:

V. DEVICE DESCRIPTION

The NEUROLINK® System is comprised of two devices, the NEUROLINK® Stent & Delivery Catheter and the NEUROLINK® Balloon Dilatation Catheter. The NEUROLINK® Stent & Delivery Catheter consists of a balloon-expandable stent that is pre-mounted on a balloon of the Delivery Catheter. The NEUROLINK® Stent is fabricated from 316L stainless steel tubing and is comprised of a series of cylindrically oriented rings aligned along a common longitudinal axis.

The NEUROLINK® Stent & Delivery Catheter is an over-the-wire, co-axial catheter design, with a balloon located at its distal end upon which the Stent is mounted. Proximal and distal radiopaque markers are positioned within the balloon to demarcate the proximal and distal edges of the NEUROLINK® Stent, and are used to facilitate accurate positioning of the stent within the target lesion. The NEUROLINK® Stent & Delivery Catheter provides a means for safely carrying the stainless steel NEUROLINK® Stent through the neurovasculature over a 0.014 inch guide wire to the target lesion for deployment. A balloon located on the distal end of the delivery catheter is designed to expand the stent to a specific diameter at a specified pressure. The distal shaft of the NEUROLINK® Stent & Delivery Catheter, excluding the NEUROLINK® Stent and the Balloon, is coated with a hydrophilic coating. At the proximal end of the catheter, a 2-port adaptation hub is incorporated to allow both guide wire insertion and contrast medium injection.

The NEUROLINK® Balloon Dilatation Catheter is very similar in design to the NEUROLINK® Stent & Delivery Catheter, except the NEUROLINK® Balloon Dilatation Catheter does not include a NEUROLINK® Stent. The distal shaft of the catheter is coated with a hydrophilic coating, which is activated when hydrated. The balloon is designed to inflate to a specific diameter and length at a specified pressure. Proximal and distal radiopaque markers are positioned within the balloon on the catheter to demarcate the proximal and distal shoulders of the balloon to facilitate accurate positioning of the balloon within an artery. At the proximal end of the catheter, a 2-port adaptation hub is incorporated to allow both guide wire insertion and contrast medium injection.

The NEUROLINK® Balloon Dilatation Catheter is used in patients who require pre-dilatation of a symptomatic atherosclerotic lesion prior to NEUROLINK® Stent placement to ensure a lumen of sufficient size for access with the NEUROLINK® Stent & Delivery Catheter; or in patients who require post-dilatation following placement of the NEUROLINK® Stent to optimize placement and apposition of the NEUROLINK® Stent implanted in a symptomatic atherosclerotic lesion.

Table 1 Device Specifications for the NEUROLINK® Stent & Delivery Catheter

Product	Stent Diameter(s) (mm)	Stent Lengths (mm)	Crossing Profile (inches)	Expanded Stent Length (mm)
NEUROLINK® Stent & Delivery Catheter <u>Inflation Pressures</u> RBP 10atm Nom. 5.5-7.0atm (8mm) Nom. 6.5-7.5atm (16mm)	2.5 3.0 3.5 4.0 4.5	8	0.044” – 0.049”	7.8 7.5 7.3 6.7 6.4
	2.5 3.0 3.5 4.0 4.5	16	0.046” – 0.051”	16.0 15.9 15.9 15.3 14.6

Table 2 Device Specifications for the NEUROLINK® Balloon Dilatation Catheter

Product	Balloon Diameter(s) (mm)	Balloon Length (mm)	Crossing Profile (inches)
NEUROLINK® Balloon Dilatation Catheter <u>Inflation Pressures</u> RBP 10atm Nom. 3.5atm–10atm	2.0 2.5 3.0 3.5 4.0 4.5 5.0	10	0.034” 0.038” 0.040” 0.044” 0.045” 0.049” 0.053”

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Treatment of recurrent ischemic stroke resulting from intracranial atherosclerosis currently includes medical therapy, percutaneous transluminal angioplasty (PTA) and surgery. Medical therapy includes use of antiplatelet and or anticoagulants and modification of atherosclerotic risk factors. Antiplatelet drugs include aspirin, Plavix (clopidogrel), or Aggrenox (dipyridamole and aspirin). Anticoagulants include warfarin. Alternative treatments used to re-establish blood flow to the brain are accomplished either by mechanically opening the atherosclerotic blockage (for example, PTA) or by surgically bypassing the affected artery.

VII. MARKETING HISTORY

The NEUROLINK® System has not been marketed in the United States or any foreign countries at the time of this submission.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects

Potential adverse events listed below may be associated with the use of the NEUROLINK® System in intracranial arteries:

Acute myocardial infarction
Death
Dissection
Drug reactions to anti-platelet or anticoagulant agents or contrast medium
Distal emboli (air, tissue or thrombotic emboli)
Fistula
Hemorrhage requiring transfusion
Hypotension/hypertension
Infection and pain at access site
Intracranial hemorrhage
Ischemia, cerebral
Pseudoaneurysm, femoral
Restenosis of stented segment
Spasm, vessel
Stent deformation
Stent embolization
Stent thrombosis/occlusion
Stroke/cerebrovascular accident
Total occlusion of an intracranial artery
Vessel perforation or rupture
Vessel spasm

Reported adverse effects

Table 3 identifies the adverse events observed in the clinical study conducted to evaluate the safety and probable benefit of the NEUROLINK® System. Sixty-one patients were enrolled in the study and information is presented on all patients through 30 days and on 48 patients who have reached the 6 month follow-up time point (see section X).

Table 3 Adverse Events

Event	# (%) (N=61)	Time of Occurrence			Device / Procedure Related		
		Proced[1]	<30 days	>30 days	Yes	No	Pending[2]
Stroke	8 (13.1%)	4[3, 4]	0	4[5]	5	2[6,7]	1
Transient Ischemic Attack (TIA)	4 (6.6%)	0	1	3	3[8]	1[9]	0
Access Site Infection	1 (1.6%)	0	1	0	1	0	0
Ankle Swelling	1 (1.6%)	0	0	1	0	1	0
Arterial Dissection	2 (3.3%)	2	0	0	2	0	0
Atrial Fibrillation	1 (1.6%)	0	0	1	0	1	0
Bradycardia	1 (1.6%)	1	0	0	1	0	0
Cancer (Pancreatic)	2 (3.3%)	0	0	2	0	0	2
Carotid Cavernous Fistula	1 (1.6%)	1[10]	0	0	1	0	0
Congestive Heart Failure	2 (3.3%)	0	1[11]	1	0	2	0
Diabetes Mellitus (new)	1 (1.6%)	0	0	1	0	1	0
Dysesthesia	2 (3.3%)	0	0	2	0	2	0
Ecchymosis (eye)	1 (1.6%)	1	0	0	1	0	0
Fractured Spine	1 (1.6%)	0	0	1	0	1	0
Kidney Stones	1 (1.6%)	0	0	1	0	1	0
Nerve Paresis (6th)	1 (1.6%)	1	0	0	1	0	0
Neurologic Symptoms	2 (3.3%)	0	0	2	1[12]	0	1[13]
Peripheral Vascular Disease	1 (1.6%)	0	0	1	0	1	0
Rehospitalized for revascularization of asymptomatic stenosis	2 (3.3%)	0	0	2	2[14, 15]	0	0
Stent Occlusion (Acute)	1 (1.6%)	1[16]	0	0	1	0	0
Syncope	2 (3.3%)	0	0	2	0	1	1
Thrombocytopenia	1 (1.6%)	0	1	0	0	1	0
Vertebral Artery Bypass	1 (1.6%)	0	0	1	1	0	0
Vertigo	3 (4.9%)	0	0	3	0	3	0

(1) Procedural' means that the event occurred at the time of the procedure or within the same hospitalization but not in excess of 30 days within the same hospitalization

(2) Event is pending adjudication by the Clinical Events Adjudication Committee (CEAC)

(3) Three strokes were adjudicated as major in severity, one as minor

(4) Two of these patients later died

(5) One of these patients later died

(6) No Stent was implanted in one of these patients. Stroke occurred five months post-procedure and is adjudicated as not related to the test device or procedure

(7) Adjudicated as not related to the test device or procedure, minor and ipsilateral, due to local microvascular thrombosis

(8) One of these TIAs was previously reported as, "possible re-emergence of stroke symptoms". CEAC adjudicated event as "TIA, probably related to test device and procedure".

(9) Per investigator, symptoms occurred after six-month angiogram and are not related to the test device, but are probably related to pre-existing condition or may be reaction to contrast dye used for the six-month angiogram.

(10) Occurred at the time of the procedure, but did not require treatment until after 30 days

(11) Exacerbation of existing congestive heart failure at 20 days post-procedure

(12) Symptoms consistent with malperfusion syndrome related to restenosis of the target lesion. Stroke and TIA ruled out. Target lesion revascularization by balloon angioplasty.

(13) Symptoms of facial droop and incontinence which resolved in 15 minutes. Ruled out stroke and TIA.

(14) Six-month angiogram demonstrated 71% in-stent restenosis; neurologic exam and stroke scale scores unchanged. Patient anxious and requested treatment. Target lesion revascularization using PTA, with residual stenosis of 46%. Follow-up unremarkable.

(15) Patient asymptomatic but restenosis determined to be "hemodynamically relevant" therefore target lesion revascularization performed with PTA.

(16) Lytic (10mg rt-PA) was administered and occlusion resolved with no clinical sequelae.

IX. SUMMARY OF PRE-CLINICAL STUDIES

Biocompatability Tests

The NEUROLINK® System was subjected to biocompatibility testing in accordance with the ANSI/AAMI//ISO 10993-1, "Biological Evaluation of Medical Devices Part I: Evaluation and Testing" standard and the May 1994 FDA *Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices: Intravascular Stents*. All tests were conducted in compliance with Good Laboratory Practices regulations (21 CFR § 58).

Useful Life (Shelf Life/Sterilization)

The NEUROLINK® System is sterilized by ethylene oxide (EO) using an overkill process resulting in a sterility assurance level (SAL) of 10^{-6}. EO and ethylene chlorohydrin residuals do not exceed limits as identified in the ANSI/AAMI//ISO 10993-7, "Biological Evaluation of Medical Devices Part 7: Ethylene oxide sterilization residuals" standard.

Product and package stability testing of the NEUROLINK® System was performed following accelerated aging and extreme conditioning. Based upon these results, an expiration date of 1 year has been established for NEUROLINK® System.

Packaging integrity testing was performed to verify that the packaging configuration for the NEUROLINK® System has met all relevant guidelines and current specifications for packaging materials.

Pyrogens

The endotoxin/pyrogen level for the NEUROLINK® System is < 0.06EU/ml per the *Guidelines for Validation of the Limulus Amebocyte Lysate Test as End-Product Endotoxin Test for Human and Animal Parental Drug, Biological Products and Medical Devices, 1987*.

Magnetic Resonance Imaging Compatibility Evaluations

The NEUROLINK® Stents are MR safe in MR systems operating at 1.5 Tesla or less, and radiofrequency (RF) energy-induced heating at a whole body averaged specific absorption rate (SAR) of 1.2 W/kg will not pose a risk to the patient implanted with a NEUROLINK® Stent. The Stent will cause image artifact.

In Vitro Bench Testing

In vitro bench testing was conducted on the NEUROLINK® System in accordance with the *Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices: Intravascular Stents*. The relevant tests outlined in the guidance were conducted to demonstrate the in vitro safety and effectiveness of the NEUROLINK® System. All test units were sterilized by ethylene oxide prior to *in vitro* bench testing. Summaries of testing conducted for the NEUROLINK® Stents, NEUROLINK® Stent & Delivery Catheter, and NEUROLINK® Balloon Dilatation Catheter follows:

NEUROLINK® Stents

Material Specification Conformance Testing*:*

Chemical Analysis:
The NEUROLINK® Stent is fabricated from medical grade 316L stainless steel tubing which conforms to ASTM F-138-92 Grade 2 in both the chemical analysis and the inclusion/ impurity content. ASTM E1086, E1019, and E112 were used to evaluate elemental composition and grain size. Scanning

Electron Microscopy (SEM) analysis was performed to identify and analyze trace surface contaminants. Tensile strength and elongation evaluations determined that the NEUROLINK® Stent met the product specifications.

ASTM Conformance:

The NEUROLINK® Stent 316L stainless steel tubing conforms to ASTM F-138-92 Grade 2 per the following ASTM Standards:

Table 4 NEUROLINK® Stent – ASTM Conformance

ASTM Standard	Title
ASTM A751-96	Practices and Terminology for Chemical Analysis of Steel Products
ASTM E1086-94	Standard Method for Optical Emission Vacuum Spectrometric Analysis of Stainless Steel by the Point to Plane Excitation Technique
ASTM E112-96e1	Standard for Determining Average Grain Size
ASTM A262-93a	Practices for Detecting Susceptibility to Inter-granular Attack in Austenitic Stainless Steel
ASTM E1019-94e1	Standard Test Method for Determination of Carbon, Sulfur, Nickel and Cobalt Alloys
ASTM E345-97e2	Standard Test Methods for Determining the Inclusion Content of Steel
ASTM F86-91	Standard Practice for Surface Preparation and Marking of Metallic Surgical Implants
ASTM G102-89 (1999)	Practice for Calculation of Corrosion Rates and related Information from Electrochemical Measurements
ASTM G5-94(1999)	Test Method for Making Potentiostatic and Potentiodynamic Anodic Polarization Measurements
ASTM G15-99b	Terminology Relating to Corrosion and Corrosion Testing

Stent Integrity Testing (8mm and 16mm length Stents):

NEUROLINK® Stent samples were measured under magnification for stent strut width, thickness, and length, stent free area percentage, length change due to expansion of the stent diameter, uniformity of expansion of the stent due to balloon inflation, percent recoil of the stent after balloon expansion, and radial hoop strength. The structural integrity of the NEUROLINK® Stents was evaluated using in vitro accelerated fatigue testing and finite element analysis modeling.

NEUROLINK® Stent & Delivery Catheter

Table 5 Summary of Functional Testing

Test	Samples		Specification	Results	
	Size	N		Size	Outcome or Mean ± SD
Delivery System Profiles Crimped Stent OD	All 8 mm sizes 2.5 x 16 mm 4.5 x 16 mm	10 ea.	≤ 0.052 mm	All 8 mm sixes 2.5 x 16 mm 4.5 x 16 mm	All samples met specification
Catheter Preparation Double-negative aspiration method with 60% contrast diluted 1:1 with water	2.5 x 8 mm 4.5 x 8 mm All 16 mm sizes	10 ea.	≤ 3 double negative preparation cycles	2.5 x 8 mm 4.5 x 8 mm All 16 mm sizes	All samples passed with 1 double negative cycle. One sample (4.5 x 8 mm) did not pass (pin hole leak) and was replaced.
Balloon Deflation Times at 10 atm (147 psi)	All 8 mm and 16 mm sizes	10 ea.	≤ 30 seconds	All 8 mm and 16 mm sizes	All samples met specification
Stent Movement - through rotating hemostatic valve, guiding catheter, and simulated 50% stenosis of 3.0mm ID tubing, lesion ID of ~1.5 mm located at radius of curvature of 0.927".	All 8 mm sizes 2.5 x 16 mm 4.5 x 16 mm	30 ea.	≤ 2 mm after 2 cycles with 95%/99% confidence/reliability	All 8 mm sizes 2.5 x 16 mm 4.5 x 16 mm	All 8 mm and 16 mm samples showed no Movement. (4) 2.5 x 16 mm units replaced due to lesions set-up error (1) 4.5 x 16 mm unit damaged replaced
Guide Catheter Stent Pullback – retraction through 6F guiding catheter	2.5x 8 mm 4.5 x 8 mm 2.5 x 16 mm 4.5 x 16 mm	15 ea.	No movement in 1 cycle with 95%/95% confidence/reliability	2.5x 8 mm 4.5 x 8 mm 2.5 x 16 mm 4.5 x 16 mm	All samples showed no movement
In-Stent Catheter Rupture at 10 atm (147 psi)	All 8 mm and 16 mm sizes	15 ea.	≥ 147 psi with 95%/99.9% confidence/reliability	All 8 mm and 16 mm sizes	All samples met specification with confidence and reliability
In-Stent Balloon Inflation Fatigue at 10 atm (147 psi)	All 8 mm sizes	15 ea.	40 cycles with 95%/90 confidence/reliability	All 8 mm sizes	All samples passed with confidence and reliability
	2.5 x 16 mm 4.5 x 16 mm	30 ea.	20 cycles with 95%/90 confidence/reliability	2.5 x 16 mm 4.5 x 16 mm	All samples passed with confidence and reliability
Stent Compliance at 10 atm (147 psi)	2.5x 8 mm 3.0 x 8 mm 3.5 x 8 mm 4.0 x 8 mm 4.5 x 8 mm 2.5 x 16 mm 3.0 x 16 mm 3.5 x 16 mm 4.0 x 16 mm 4.5 x 16 mm	15 ea.	2.65 mm 3.24 mm 3.72 mm 4.34 mm 4.86 mm 2.75 mm 3.27 mm 3.86 mm 4.31 mm 4.81 mm	2.5x 8 mm 3.0 x 8 mm 3.5 x 8 mm 4.0 x 8 mm 4.5 x 8 mm 2.5 x 16 mm 3.0 x 16 mm 3.5 x 16 mm 4.0 x 16 mm 4.5 x 16 mm	All samples met specification
Inner Member Collapse	2.5 x 16 mm 4.5 x 16 mm	30 ea.	Reversible at 10 atm (147 psi)	2.5 x 16 mm 4.5 x 16 mm	All samples met specification
Shaft Tensile Strength - Proximal luer adaptor and distal catheter shaft	2.5 x 16 mm 4.5 x 16 mm	10 ea.	≥ 1.0 lbs.	2.5 x 16 mm 4.5 x 16 mm	All samples met specification
Proximal Adaption Tensile Strength	2.5 x 16 mm 4.5 x 16 mm	10 ea.	≥ 1.0 lbs.	2.5 x 16 mm 4.5 x 16 mm	All samples met specification
Proximal Balloon Seal Tensile Strength - Proximal balloon seal to the distal outer member junction	All 8 mm sizes 2.5 x 16 mm 4.5 x 16 mm	10 ea.	≥ 1.0 lbs	All 8 mm sizes 2.5 x 16 mm 4.5 x 16 mm	All samples met specification
Soft Tip Tensile Strength - Distal balloon seal to soft tip junction	2.5 x 16 mm 4.5 x 16 mm	10 ea.	≥ 0.5 lbs	2.5 x 16 mm 4.5 x 16 mm	All samples met specification

Table 6 Summary of Functional Testing

Test	Samples		Specification	Results	
	Size	N		Size	Outcome or Mean ± SD
Delivery System Profile-2/3 Balloon Profile	All sizes	10 ea.	≤ 0.053 mm	All sizes	All samples met specification
Catheter Preparation: Double-negative aspiration method with 60% contrast diluted 1:1 with water	All sizes	10 ea.	≤ 3 double negative preparation cycles	All sizes	All samples passed with 1 double negative cycle.
Balloon Deflation Times at 10 atm (147 psi)	All sizes	10 ea.	≤ 30 seconds	All sizes	All samples met specification.
Catheter Rupture (Out of Stent) at 10 atm (147 psi)	2.0x 10 mm 4.0 x 10 mm 4.5 x 10 mm 5.0 x 10 mm	15 ea.	≥ 186 psi with 95%/99.9% confidence/reliability	2.0x 10 mm 4.0 x 10 mm 4.5 x 10 mm 5.0 x 10 mm	Each size passed with confidence and reliability
Catheter Rupture (In-Stent) at 10 atm (147 psi)	2.0x 10 mm 2.5x 10 mm 3.0 x 10 mm 3.5 x 10 mm 4.0 x 10 mm 4.5 x 10 mm 5.0 x 10 mm	15 ea. 19	≥ 147 psi with 95%/99.9% confidence/reliability	2.0x 10 mm 2.5x 10 mm 3.0 x 10 mm 3.5 x 10 mm 4.0 x 10 mm 4.5 x 10 mm 5.0 x 10 mm	Each size passed with confidence and reliability
In-Stent Balloon Inflation Fatigue at 10 atm (147 psi)	2.0x 10 mm 4.0 x 10 mm 4.5 x 10 mm 5.0 x 10 mm	30 ea.	20 cycles with 95%/90 confidence/reliability	2.0x 10 mm 4.0 x 10 mm 4.5 x 10 mm 5.0 x 10 mm	Each size passed with confidence and reliability
Balloon Compliance at 10 atm (147 psi)	2.0x 10 mm 2.5x 10 mm 3.0 x 10 mm 3.5 x 10 mm 4.0 x 10 mm 4.5 x 10 mm 5.0 x 10 mm	15 ea.	2.04 mm 2.51 mm 3.06 mm 3.52 mm 4.14 mm 4.61 mm 5.17 mm	2.0x 10 mm 2.5x 10 mm 3.0 x 10 mm 3.5 x 10 mm 4.0 x 10 mm 4.5 x 10 mm 5.0 x 10 mm	All samples met specification
Proximal Balloon Seal Tensile Strength - Proximal balloon seal to the distal outer member junction	2.0x 10 mm 4.0 x 10 mm 4.5 x 10 mm 5.0 x 10 mm	10 ea.	≥ 1.0 lbs	2.0x 10 mm 4.0 x 10 mm 4.5 x 10 mm 5.0 x 10 mm	All samples met specification
Soft Tip Tensile Strength - Distal balloon seal to soft tip junction	2.0x 10 mm 4.0 x 10 mm 4.5 x 10 mm 5.0 x 10 mm	10 ea.	≥ 0.5 lbs	2.0x 10 mm 4.0 x 10 mm 4.5 x 10 mm 5.0 x 10 mm	All samples met specification
Coating Friction	4.0 x 10 mm	10	≤ 0.157 Coefficient of Friction	4.0 x 10 mm	All samples met specification
Coating Dry Adhesion	4.0 x 10 mm	10	≤ 0.20% Loss ≥ 80% Adhesion	4.0 x 10 mm	0.0 ± 0.0 % Loss 100 ± 0.0 % Adhesion
Coating Particulate	4.0 x 10 mm 5.0 x 10 mm	10 ea.	≤ 200 particulates > 0.02 mm2	4.0 x 10 mm 5.0 x 10 mm	No particulates counted > 0.02 mm2

Animal Studies

Preclinical evaluations in swine were conducted with the NEUROLINK® System and included acute and chronic studies. The acute performance using angiography included the evaluation of the trackability, accessibility, deployment accuracy, uniformity of stent expansion and device compatibility of the NEUROLINK® Stent & Delivery Catheter, and the NEUROLINK® Balloon Dilatation Catheter. The acute performance of the System was rated as above average when compared to the investigator's experience with other balloon-expandable stent systems. Angiography at 3 and 28 days post-implant revealed patent lumens and TIMI 3 flow for both the 8 mm and 16 mm NEUROLINK® Stents (TIMI, or Thrombolysis In Myocardial Infarction, is a grading system to describe blood perfusion, with Grade 0 representing no perfusion and Grade 3 representing complete perfusion). At 28 days, all of the 20 implanted stents were fully patent with two (2) of the 8 mm stents exhibiting mild to moderate stenosis and four (4) of the 16 mm stents exhibiting mild stenosis. Histology studies, including light microscopy, gross tissue evaluation, and morphometry, was performed at 3 and 28 days in the chronic studies of the 8 mm and 16 mm NEUROLINK® Stents. With the exception of one (1) stented vessel at the 28-day time point which showed >50% stenosis, vessels examined revealed mild stenosis, mild vessel injury, and mild to mild/moderate medial compression. The vessels stented with the 16 mm stent showed mild stenosis, mild vessel injury with the exception of two (2) vessels with focal moderate injury, and mild to moderate medial compression. Scanning electron microscope (SEM) analysis was performed for one sample obtained from the 8 mm NEUROLINK® Stent at 28 days. The stent appeared equally expanded within the lumen and the struts were well apposed to the wall. The stent was completely covered with a thin layer of neointima comprised of spindle and polygonal shaped endothelial cells.

In separate studies, procedural performance of the device was evaluated in a total of forty-eight (48) NEUROLINK® Stent and Delivery Catheters and six (6) NEUROLINK® Balloon Dilatation Catheters. The devices were delivered and deployed in the left and right internal mammary arteries, left and right external carotid arteries, right coronary artery, lateral anterior descending artery, left anterior descending artery, right renal artery, and the right and left brachial arteries with a stent-to-artery ratio ranging between 1.0: 1 to 1.2: 1. A total of thirteen (13) pigs were used in five (5) separate studies. The safety and performance was evaluated angiographically for acute and long-term (28 days) studies and histologically for the long-term (28 days) implants. These studies revealed no complications during introduction of the devices through RHV (rotating hemostatic valves) and 6F guides, minimal resistance to contrast injection, ability to access distal anatomy, clinically acceptable radiopacity of the stent, good stent apposition to vessel walls, no angiographic evidence of vessel injury, and TIMI 3 flow.

X. SUMMARY OF CLINICAL INFORMATION

SSYLVIA: Stenting of SYmptomatic atherosclerotic Lesions in the Vertebral and Intracranial Arteries

The NEUROLINK® System was designed for the treatment of atherosclerotic disease in the neurovasculature. The SSYLVIA clinical study is a prospective, non-randomized, multi-center, international study and is ongoing. The objective of the study is to evaluate the safety and feasibility of the NEUROLINK System for the treatment of symptomatic atherosclerotic lesions in the extracranial vertebral and intracranial arteries. Patients were eligible for participation in the study if they were symptomatic (previous stroke or TIA) due to an angiographically demonstrated, discrete stenosis >50% and ≤5mm in length in an extracranial vertebral or intracranial artery between 2.5mm and 4.5mm in diameter. The clinical study evaluated stent use in a broader patient population than that characterized in the Humanitarian Use Device (HUD) designation.

All patients were required to receive an antiplatelet regimen beginning at least 48 hours prior to the procedure. This consisted of aspirin (minimum 100mg twice daily) and Clopidogrel (75mg twice daily). Heparin was administered during the Stent implantation procedure to maintain the activated clotting time (ACT) at a therapeutic level of 200 to 300 seconds.

The NEUROLINK® Balloon Dilatation Catheter could be used to predilate the lesion to facilitate access by the NEUROLINK Stent and Delivery Catheter. Both the Balloon and Stent were sized in a 1:1 ratio to the smaller of the diameters of the vessel proximal or distal to the lesion. Post-dilatation with either the Delivery Catheter or the Balloon Dilatation Catheter could be used to optimize Stent apposition and residual stenosis.

Post-procedure, dual antiplatelet therapy was required. This consisted of aspirin daily for a minimum of one (1) year, plus Clopidogrel for a minimum of four (4) weeks. Device and procedural safety were determined by analyzing acute and 30-day individual endpoints, and all adverse events. All primary endpoints were analyzed on an intent-to-treat basis.

The primary endpoints for safety are clinical outcome at 30 days (composite stroke and death), and clinical and angiographic outcome at 6 months. Clinical outcome data is reported for the combined patient population of extracranial vertebral and intracranial lesions.

All patients are required to have independent neurologic examinations (performed by the non-operator stroke neurologist investigator) at one, three, six, and 12 months. Angiographic assessment of the stented lesion is required at six months. All procedure and follow-up angiograms are analyzed by an independent Angiographic Core Laboratory. Major clinical events are adjudicated by an independent Clinical Events Adjudication Committee. The Data Safety Monitoring Board (DSMB) is responsible for review of the cumulative safety data at scheduled intervals, to ensure subject safety.

Patient Data Available

Sixty-one (61) patients were enrolled in the study. Results are presented on all patients through 30 day follow-up. Data is presented for the 48 patients who have reached 6 month follow-up. Adverse events are reported for all patients in Table 3.

Table 7. Summary of Patient Data Available

Visit Type	Patient Data Available*	Percent of Total (N=61)
Pre-procedure	61	100%
Procedure	61	100%
Discharge	61	100%
30-day Follow-up	61	100%
3-month Follow-up	54	88.5%
6-month Clinical Follow-up	48	78.7%
6-month Angiogram	42	68.9%

Table 8. Patient Demographics: Age Sex, and Neurological History

Patient Characteristics	
Age (years)[1]	
Mean ± SD	63.4 ± 9.8
Median	64
Range (min, max)	(37, 80)
Male	80.3%
Transient Ischemic Attack	68.9% (42/61)
Stroke	60.7% (37/61)
Other Neurological Disease currently being treated or requiring treatment [2]	3.3% (2/61)

[1] Data available through Age statistics based on 58 patients

[2] Back injury in one patient causing back and right leg pain. Bladder dysfunction, described by the investigational site as attributable to neurologic deficit in one patient.

Table 9 Medical History: Cardiac

Cardiac Risk Factor	Percent with Risk Factor
Hypertension	63.9% (39/61)
Coronary Artery Disease (CAD) Intervention	13.1% (8/61)
Angina	11.5.% (7/61)
Myocardial Infarction	11.5% (7/61)
Arrhythmia	3.3% (2/61)
Atrial Fibrillation	3.3% (2/61)
Other Cardiac[1]	3.3% (2/61)
Patent Foramen Ovale	3.3% (2/61)
Congestive Heart Failure	1.6% (1/61)
Surgical Intervention Planned[2]	1.6% (1/61)

[1] Aortic valve replacement in one patient, mild mitral valve insufficiency
[2] Cardiac catheterization

Table 10 Medical History: Other

Risk Factors	Percent with Risk Factor
Hypercholesterolemia	54.1% (33/61)
Smoking (current or former)	52.5% (32/61)
Diabetes	32.8% (20/61)
Hereditary or Racial Risk	18.0% (11/61)
Pulmonary Disease: Other*	13.1% (8/61)
Cancer	6.6% (4/61)
Other Significant Risk Factors	4.9% (3/61)
Pulmonary Disease: COPD	4.9% (3/61)
Substance Abuse	4.9% (3/61)
GI Bleed	1.6% (1/61)

*pulmonary cancer, asbestos exposure, sleep apnea, emphysema, possible tuberculosis, dyspnea and asthma (two)

Baseline lesion locations are listed in Table 11. Of the 61 subjects, six (6) lesions were in the vertebral ostium and 12 in the pre-posterior inferior cerebellar artery (PICA) region of the vertebral artery. These two lesion types were classified as extracranial. Thus, there were 43/61 (70.5%) intracranial lesions, and 18/61 (29.5%) extracranial vertebral lesions.

Table 11. Primary Lesion Location

Primary Lesion Location	# Patients	% of Total (N=61)
Intracranial		
Basilar – proximal	11	18.0%
Basilar – mid	6	9.8%
Internal Carotid – Cavernous	7	11.5%
Intracranial Vertebral – post PICA	5	8.2%
Internal Carotid – Supraclinoid	6	9.8%
Middle Cerebral	5	8.2%
Internal Carotid – Petrous	2	3.3%
Posterior Cerebral	1	1.6%
Total Intracranial	43	70.5%
Extracranial		
Extracranial Vertebral – pre PICA	12	19.7%
Extracranial Vertebral Ostium	6	9.8%
Total Extracranial	18	29.5%

Primary Endpoints

The primary endpoints for safety are clinical outcome at 30 days (composite stroke and death), and clinical and angiographic outcome at 6 months. Clinical outcome data is reported for the combined patient population of extracranial vertebral and intracranial lesions.

Table 12. Primary Endpoints

Primary Endpoints	(N=61)	
	# Patients	% Incidence
Death and Stroke (composite) at 30 days	4	6.6%
Non-Fatal Stroke at 30 days [1]	4	6.6%
Major stroke	3	4.9%
Minor stroke	1	1.7%
Death at 30 days	0	0%
Death and Stroke (composite) > 30 days	8	13.2%
Non-Fatal Stroke > 30 days	4	6.6%
Major stroke	1[4]	1.7%
Minor stroke	3	4.9%
Death > 30 days	4[5]	6.6%
Acute Success Measures		
Stent Success [2]	58	95.1%
Procedure Success[3]	54	88.5%

[1] The CEAC determined that three of the four strokes were major and one stroke was minor. The distinction of Major stroke and Minor stroke is based on the NIHSS and/or Modified Rankin Score and/or Barthel Index score at 30 days post-stroke.
[2] Stent Success is defined as achieving a final residual stenosis <50% covering an area no longer than the original lesion. Results are based on Core Lab measurements for fifty-three (53) patients and on investigator measurements for the patients for whom data is not available.
[3] Procedure Success is achieved if there was Stent Success and no death or stroke prior to discharge.
[4] This patient later died
[5] Two (2) patients had non-fatal major strokes within 30 days of treatment, one (1) patient died of metastatic pancreatic cancer at one year post procedure, one (1) patient suffered a major stroke at one year post-procedure.

Secondary Endpoints

The secondary endpoints include access site complications requiring treatment, angiographic evaluation of the treated segment at six months, and ipsilateral (same territory) stroke at 12 months.

Access Site Complications: There was one access site infection that required treatment, for an incidence rate of 1.6% (1/61).

Angiographic Evaluation at 6 months: Forty-eight (48) patients have completed their six month follow-up. The minimum lumen diameter increased from a mean of 1.00mm at pre-procedure, to a mean of 1.64mm. The percent stenosis decreased from a mean of 69.9% pre-procedure, to a mean of 50.6% at six months. Eighteen (18) patients had stenoses >50% at 6 months and seven of these (38.9%) were symptomatic, while 11 (61.1%) were asymptomatic.

Ipsilateral stroke at 12 months: The mean follow-up was 216 days , with a minimum and maximum follow-up of 2 and 367 days, respectively. Within this follow-up period, there were four (4) strokes. Four (4) procedure-related strokes occurred; three of these strokes were major and ipsilateral, and one was minor and contralateral. Four (4) strokes occurred after 30 days. Three of these strokes were adjudicated as ipsilateral and minor. The fourth stroke is pending adjudication, and will be assumed to be ipsilateral for the purpose of this analysis. Therefore, the lower limit of the rate of ipsilateral stroke at 12 months for this patient population is 11.5% (7/61).

Table 13. Lesion Characteristics

This data compares independent angiographic core laboratory measurements of lesion characteristics pre-procedure, post-procedure, and at 180 days (6 months) for the combined patient group with extracranial vertebral and intracranial lesions. Subgroup analysis is provided for intracranial lesions only.

Parameter	Baseline [1]		Post-Procedure [1]		6 Months	
	All Vessels (N=60)	Intracranial Only (N=42)	All Vessels (N=60)	Intracranial Only (N=42)	All Vessels (N=42) [7]	Intracranial Only (N=27)
Lesion Length (mm) [2]						
Mean ± SD	5.10 ± 1.91	5.15 ± 1.91				
Median	4.80	4.85				
Range (min, max)	(1.5, 9.9)	(1.5, 9.9)				
Reference Vessel Diameter (mm)						
Mean ± SD	3.29 ± 0.70	3.29 ± 0.74	3.32 ± 0.68	3.30 ± 0.71	3.30 ± 0.61	3.29 ± 0.65
Median	3.30	3.35	3.35	3.40	3.35	3.30
Range (min, max)	(1.7, 4.7)	(1.7, 4.6)	(1.9, 5.0)	(1.9, 4.7)	(2.0, 4.4)	(2.0, 4.4)
MLD at Stenosis (mm)						
Mean ± SD	1.00 ± 0.46	0.95 ± 0.45	2.63 ± 0.72	2.62 ± 0.69	1.64 ± 0.94	1.90 ± 0.98
Median	1.00	0.90	2.50	2.50	1.65	1.80
Range (min, max)	(0.0, 2.3)	(0.0, 2.0)	(1.4, 5.1)	(1.5, 4.2)	(0.0, 4.2)	(0.4, 4.2)
Gain in MLD from Baseline (mm) [3][6]						
Mean ± SD			1.62 ± 0.75	1.68 ± 0.72	1.5 ± 0.9	1.89 ± 0.1
Median			1.60	1.75	1.4	1.8
Range (min, max)			(0.1, 3.7)	(0.5, 3.7)	(-1.3, 2.5)	(-0.5, 3.7)
Percent Stenosis						
Mean ± SD	69.9% ± 12.41	71.1% ± 13.08	20.3% ± 15.38	19.7% ± 15.66	50.6% ± 25.6	43.4% ± 24.1
Median	70.2%	70.7%	16.67%	16.24%	44.8%	42.4%
Range (min, max)	(42% [4], 100%)	(42% [4], 100%)	(-9.1%, 56.3%)	(-9.1%, 50.0%)	(0%, 100%)	(0.0%, 84.4%)
Change in % Stenosis from Baseline [5][6]						
Mean ± SD			+49.6% ± 20.44	+51.3% ± 19.79	+17.1% ± 28.0	+26.4% ± 26.7%
Median			46.75%	52.45%	44.8%	42.4%
Range (min, max)			(3.1%, 100%)	(17.9%, 100%)	(+63.5%, -50%)	(-15.3%, 90.2%)
# >50% Stenosis	57 / 60 (95%)	40/42 (95%)	1 / 60 (1.6%)	1 / 42 (2.6%)	18 / 42 (42.9%)	10 / 27 (37%)

(1) All data is from core lab when available. For seven patients without core lab data, the physician measurements were used.

(2) Twenty-one (21) of 53 lesions measured by the core lab exceeded 5mm length pre-procedure. In all instances the investigator had measured the lesion as ≤5mm pre- procedure, qualifying the patients for study enrollment. Sixteen (16) of these lesions were intracranial.

(3) Acute gain is defined as the difference in Minimum Lumen Diameter (MLD) between the pre- and post-procedure. A positive number indicates that the lumen is larger after the procedure.

(4) The core lab measured three lesions as <50% stenosis pre-procedure. Investigators measured these lesions as 50%, 53%, and 63%, respectively, qualifying the patients for study enrollment. Two of these were intracranial lesions.

(5) Change is pre-treatment value minus post-treatment value, therefore a positive number denotes a decrease in percentage stenosis.

(6) A negative number for MLD or % stenosis indicates an increase in lumen diameter or a reduction in % stenosis.

(7) Four of 6 patients with lesions of the extracranial vertebral ostium had asymptomatic total occlusion at follow-up angiography.

XI. RISK/PROBABLE BENEFIT ANALYSIS

Recurrent stroke attributable to intracranial atherosclerosis refractory to medical therapy is associated with a poor prognosis. This is the patient group characterized in the HUD designation. The poor prognosis is related to additional strokes and clinical events due to atherosclerosis in other arterial locations. Mechanisms for these additional strokes include reduced blood flow secondary to decrease in arterial diameter and arterial to arterial embolism based on plaque morphology. Stents have been shown to increase arterial diameter in a variety of arterial locations and to reduce arterial-to-arterial embolism by altering plaque morphology.

Mechanical and animal model performance evaluations of the stent (sizes 8 and 16 mm), the balloon catheter and the stent delivery catheter were conducted. The mechanical evaluations determined that the NEUROLINK® System had sufficient device physical attributes for the intended use of the product. The preclinical animal model evaluations showed that the System was comparable to other percutaneous catheter-based interventional products in handling and placement characteristics. The acute and chronic time point assessments regarding histological and angiographically-determined endpoints indicated that the stent was biocompatible and that it maintained a patent lumen. Although the clinical study only evaluated the 8 mm stent, the 16 mm stent was evaluated in preclinical and animal testing. The results of the testing with the 16 mm stent were comparable to the results obtained with the 8 mm stent. Based on these results, it was concluded that the 16 mm stent would be expected to perform similarly to the 8 mm stent in clinical use.

The sponsor has completed a clinical study in 61 patients with symptomatic extracranial vertebral and intracranial atherosclerosis. Data obtained for stent use in this more broadly defined patient group is applicable to the evaluation of safety and probable benefit of the HUD patient group.

Clinical and angiographic follow-up was completed at 6 months for 48 patients. Pre-dilation of the target lesion and/or post-stent deployment dilation was performed as clinically indicated. For comparison, information from two retrospective studies of the same type of patient population treated under traditional medical therapy was used. In the Warfarin-Aspirin Intracranial Disease Study [(1)], the rate of fatal and non-fatal stroke was 14.6% and total stroke/death rate was 22.5% (follow-up of 15-19 months). In the Stanford Study[(2)] the rate of fatal and non-fatal stroke was 24.1% and all stroke and death was 27.5% (mean follow-up of 14.6 months). Therefore in these studies, the incidence of stroke ranges from 14.6% to 24.1% and the death rate ranges from 6.8% to 11.7%. The composite rates range from 22.5% to 27.5%. The data is representative of events occurring over a 14.6 to 19.3 month time line. The composite death and stroke rate observed in the SSYLVIA study was 13.2%. Therefore, there was an apparent reduction in the death and stroke rate of patients treated with the NEUROLINK® System. An increase in arterial diameter was also demonstrated by angiography in the SSYLVIA study. The binary angiographic restenosis rate (>50%) needs to be interpreted in the context of the clinical event rate. Dissociation between clinical outcome and angiographic findings in the treatment of coronary artery disease has been recognized for a number of years.

Adverse events are noted in Table 3. No unanticipated adverse events were noted. A total of 8 strokes occurred. Four strokes were considered device- or procedure-related and occurred at the time of stent placement. The other 4 occurred after 30 days of follow-up. The type and frequency of other adverse events are consistent with those generally reported for percutaneous catheter-based interventions in the neurovasculature and other arterial locations.

Data for patient outcome at 30 days and 6 months was combined for both symptomatic extracranial vertebral and intracranial lesions in the evaluation for the intended stent use. Although the NEUROLINK System is indicated for only intracranial lesions, data from the treatment of patients with extracranial lesions supports the conclusion that the frequency of adverse events experienced with this device is low.

Therefore, it is reasonable to conclude that the probable benefit to health from using the NEUROLINK System for intracranial stenting for recurrent stroke attributable to intracranial atherosclerosis refractory to medical therapy outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment, when used as indicated in accordance with the directions for use.

XII. PANEL RECOMMENDATION

Review of this application was performed by FDA and by a member of the Neurological Devices Advisory Panel. The NEUROLINK® Stent (8 mm and 16mm) are very similar in design and device materials to the approved ACS MULTILINK™ Coronary Stent and the ACS MULTILINK DUET™ Coronary Stent and it was determined that the clinical issues raised by the HDE did not require full Panel review.

XIII. CDRH DECISION

CDRH determined that, based on the data submitted in the HDE, the NEUROLINK® System will not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from using the device for the treatment of patients with recurrent intracranial stroke attributable to atherosclerotic disease refractory to medical therapy in intracranial vessels ranging from 2.5 to 4.5 mm in diameter with = 50% stenosis and that are accessible to the stent system outweighs the risks of illness or injury, and issued an approval order on August 9, 2002.

XIV. APPROVAL SPECIFICATIONS

INDICATIONS FOR USE: See Labeling (Attachment 1)

INFORMATION FOR THE PATIENT: See Patient Brochure (Attachment 2)

HAZARDS TO HEALTH FROM USE OF THIS DEVICE: See Indications, Contraindications, Warnings and Precautions, and Adverse Events in the labeling.

XV. REFERENCES

1. Chimowitz, M.I., Kokkinos, J. and Fayad, P.B. "The Warfarin-Aspirin Symptomatic Intracranial Disease Study". Neurology 45: 1488-93, 1995.

2. Thijs, V.N. and Albers, G.W. "Symptomatic intracranial atherosclerosis: outcome of patients who fail antithrombotic therapy," Neurology 55(4):490-7, 2000.